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CRESTONE – Clinical Study of REsponse to Seribantumab in Tumors with NEuregulin-1 (NRG1) Fusions – A Phase 2 Study of the anti-HER3 mAb for Advanced or Metastatic Solid Tumors (NCT04383210)

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NRG1 fusions are rare oncogenic drivers

- NRG1 (Neuregulin-1) gene fusions are rare oncogenic drivers found in 0.2% of solid tumors, including lung, pancreatic, gallbladder, breast, ovarian, colorectal, neuroendocrine, and sarcomas.[1,2]
- NRG1 is the predominant ligand of HER3 and to a lesser extent HER4.
- NRG1 fusion proteins retaining an active EGF-like domain drive tumorigenesis and proliferation through aberrant HER3 activation (**Fig 1**).

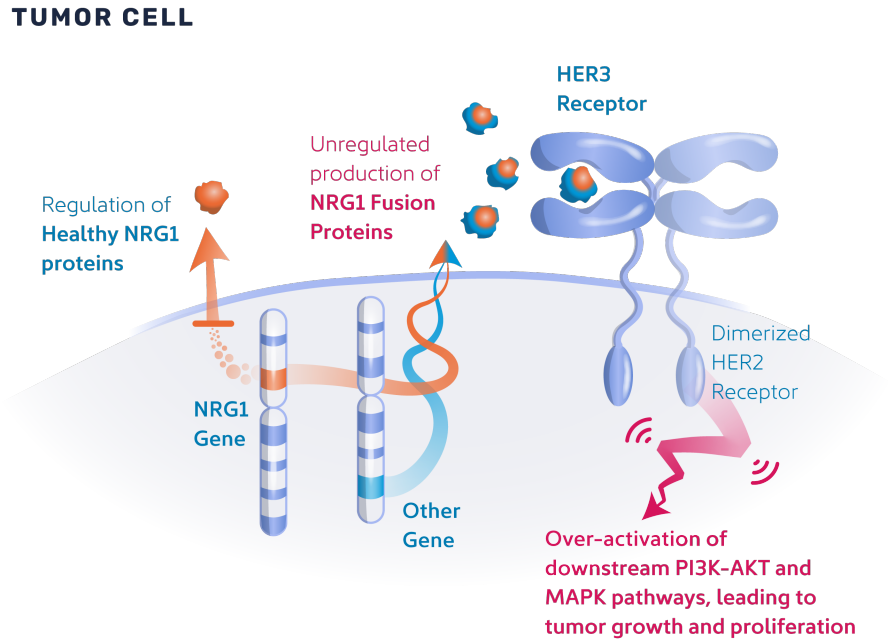

Figure 1. NRG1 fusion activation of HER3 and downstream pathways

New targeted therapies are needed for the treatment of solid tumors with an NRG1 fusion

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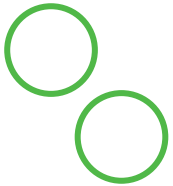
Standard of Care

Patients with NRG1 fusions **do not normally respond well to treatment** with standard chemotherapy, chemoimmunotherapy or novel checkpoint inhibitors such as anti-PD-1/anti-PD-L1 therapies.[5]

OS & DFS

Presence of an NRG1 fusion has been correlated with **worse overall and disease-free survival** when treated with current therapies.[6]



Exclusive with known drivers

Importantly, NRG1 fusions are often **mutually exclusive with other known driver alterations**.[2,3,4]

NRG1 fusions are actionable biomarkers in pancreatic cancer

- NRG1 fusions are estimated to appear in 2% of pancreatic cancers overall.[7]
- NRG1 fusions are enriched in the pancreatic ductal adenocarcinoma (PDAC) subtype, where the incidence may be as high as 6%.[8]
- NRG1 fusions appear to be mutually exclusive with KRAS activating mutations.[8,9]
- Published clinical case reports of pancreatic tumors harboring NRG1 fusions suggest that **significant responses can be achieved through inhibition of ERBB family members** (**Table 1**).

Table 1. Clinical case reports of responses in NRG1 fusion positive PDAC

Tumor Type	NRG1 Fusion	Response (DoR, mths)	Ref
Afatinib (Pan-HER TKI)			
KRAS-wt Stage IV PDAC with liver metastases	APP – NRG1	PR (7+, ongoing)	[10]
KRAS-wt Stage IV PDAC with liver metastases	ATP1B1 – NRG1	PR (5.5)	
KRAS-wt, Stage IV PDAC	ATP1B1 – NRG1	PR (< 5)	[9]
Erlotinib (EGFR TKI) **+ Pertuzumab** (mAb preventing dimerization of HER2)			
KRAS-wt, Stage IV PDAC	SARAF – NRG1	PR (< 5)	[9]
MCLA-128 (HER2/HER3 bispecific antibody)			
KRAS-wt Stage IIB PDAC	ATP1B1 – NRG1	PR (7+, ongoing)	[11]
KRAS-wt Stage IV PDAC with liver metastases	ATP1B1 – NRG1	PR (7+, ongoing)	

Seribantumab (anti-HER3 IgG2 mAb)

- Seribantumab is a fully human IgG2 mAb inhibiting HER3 and downstream pathways through:
  - Inhibition of NRG1-dependent activation of HER3,
  - Inhibition of HER3-HER2 dimerization, and
  - Blocking signaling through the PI3K/AKT and MAPK pathways.
- The safety profile of seribantumab is well characterized through prior monotherapy (N=43) and combination studies in over 800 patients.

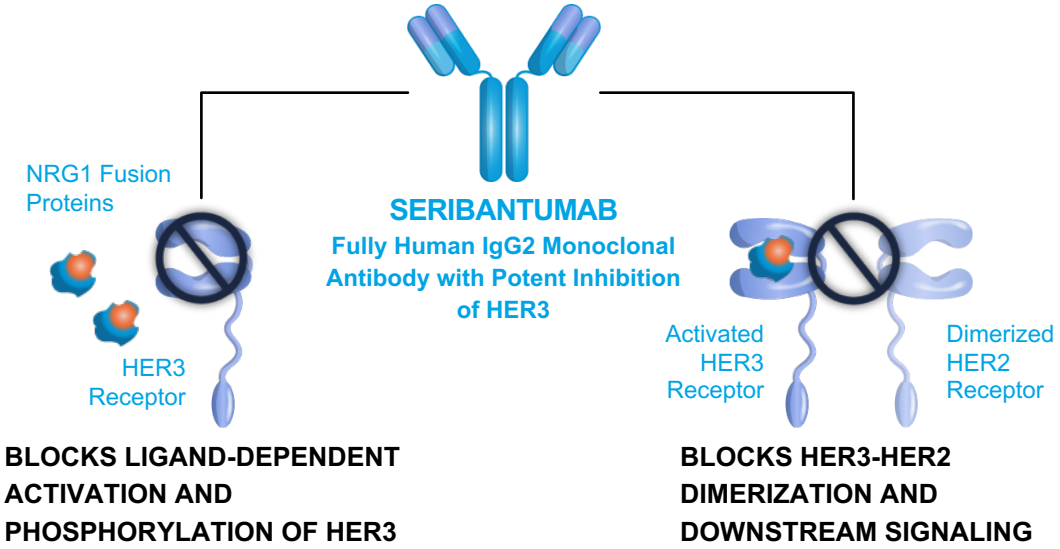


Figure 2. Seribantumab inhibition of HER3 and downstream pathways

CRESTONE: Ph 2 tumor-agnostic basket trial

- Open label, multicenter Phase 2 basket trial of seribantumab in adult patients with NRG1 fusion-positive locally advanced or metastatic solid tumors who have progressed on or are nonresponsive to available therapies.
- Enrolling N=75 patients across three cohorts:
  - **Cohort 1** (N=55): Patients who have not received prior treatment with any ERBB targeted therapy.
  - **Cohort 2** (up to N=10): Patients who have progressed after prior treatment, including prior ERBB targeted therapy.
  - **Cohort 3** (up to N=10): Patients harboring NRG1 fusions without an EGF-like binding domain.
- Novel dosing regimen designed to rapidly achieve steady state levels, optimize exposure, and deliver maximal NRG1 inhibition.

Phase 2 Tumor-Agnostic Trial

Age ≥18 years old | Advanced solid tumors

NRG1 fusion positive by local CLIA or similarly accredited lab

PIVOTAL Cohort 1	EXPLORATORY Cohort 2	EXPLORATORY Cohort 3
*N = 55**	*N = 10*	*N = 10*
No prior treatment with Pan-ERBB, HER2, HER3 targeted therapy	Relapsed/Refractory following treatment with Pan-ERBB, HER2, or HER3 targeted therapy	NRG1 fusions without EGF-like domain OR Insufficient tissue for central confirmatory testing
**Interim analysis at N = 20 with centrally confirmed NRG1 fusion*		

Investigational Therapy: Seribantumab (IV)		
Induction (weekly)	**Consolidation (biweekly)**	**Maintenance (Q3W)**
Weeks 1-4: 3g weekly	6 cycles, 3g Q2W	3g Q3W until PD or toxicity

CRESTONE: Key eligibility criteria

Key Inclusion Criteria

- ✓ **Locally-advanced or metastatic solid tumor with an NRG1 gene fusion**
- ✓ Fresh or archived FFPE tumor sample
- ✓ Minimum of one prior standard therapy
- ✓ ≥ 18 years of age
- ✓ ECOG performance status: 0, 1, or 2
- ✓ At least one measurable extra-cranial lesion (RECIST)

Key Exclusion Criteria

- ○ Known, actionable oncogenic driver mutation other than NRG1 fusion where available standard therapy is indicated

NRG1 fusion status for enrollment will be determined through a local CLIA or similarly accredited molecular assay.

NRG1 fusion status for patients in Cohort 1 will be centrally confirmed using an RNA-based NGS assay.

CRESTONE: Study objectives

Primary endpoint

Objective response rate (ORR) per RECIST v1.1 by independent/central radiologic review.

Secondary endpoints

- Duration of response (DoR)
- Safety
- Progression free survival (PFS)
- Overall survival (OS)
- Clinical Benefit Rate (CR, PD, SD > 24 weeks)

Exploratory endpoints

- Clinical relevance of fusion partners
- Impact of prior therapies, including ERBB targeted therapies
- Resistance mechanisms

CRESTONE: Study status

CRESTONE is open and enrolling with 25-30 planned sites in the US.

Patient identification and enrollment is enhanced through partnerships enabling targeted patient identification and ”Just in Time” site initiation.

Open sites as of September 7, 2020		
Site		**Investigator**
SARAH CANNON	Sarah Cannon	Johanna Bendell, MD
SITEMAN CANCER CENTER	Washington University at St. Louis (Siteman Cancer Center)	Saiama N. Waqar, MD
Henry Ford Health System / Henry Ford Cancer Institute	Henry Ford Health System	Shirish Gadgeel, MD
Carbone Cancer Center, University of Wisconsin School of Medicine and Public Health	University of Wisconsin (Carbone Cancer Center)	Mark E. Burkard, MD, PhD

Partnerships as of September 7, 2020

ASHION (A TGen Clinical Laboratory) · CARIS LIFE SCIENCES · STRATA oncology · TEMPUS · US Oncology Research

Summary

- NRG1 fusions are an actionable driver alteration across solid tumors and appear to be mutually exclusive with KRAS activating mutations in PDAC.
- Inhibition of HER3 and its dimerization partners represents a rational and novel therapeutic approach for tumors harboring an NRG1 fusion, supported by case studies of clinical responses to therapies targeting ERBB family members.[4,5,8,9,10,11]
- CRESTONE is a Phase 2 tumor agnostic study of seribantumab, an anti-HER3 antibody, in patients with solid tumors that harbor an NRG1 fusion.

Learn more about CRESTONE (NCT#04383210) at www.nrg1fusion.com

Contact: clinical@elevationoncology.com or medicalaffairs@elevationoncology.com

References

1. Jonna et al., Journal of Clinical Oncology. 2020 May 20; 38(15__suppl):3113-3113.
2. Jonna et al., Clin Cancer Res. 2019 Aug 15;25(16):4865-4867.
3. Fernandez-Cuesta L and Thomas RK., Clin Cancer Res. 2015 May 1; 21(9):1989-94
4. Drilon A et al., Cancer Discov. 2018 Jun;8(6):686-695.
5. Duruisseaux M et al., ASCO 2019, Abstract 9081.
6. Shin DH et al., Oncotarget. 2016 Oct 25;7(43):69450-69465.
7. Stalbovskaya V et al., J Clin Oncol 38: 2020 (suppl; abstr e15605).
8. Jones MR et al., Clin Cancer Res. 2019 Aug 1;25(15):4674-4681.
9. Heining C et al., Cancer Discov. 2018 Sep;8(9):1087-1095.
10. Weinberg BA et al., ESMO 2019.
11. Schram AM et al., AACR-NCI-EORTC 2019, Abstract PR02.